Mechanisms of vascular dysfunction in mice with endothelium-specific deletion of the PPAR-delta gene.

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Public Summary:
Peroxisome proliferator-activated receptor (PPAR)- is a nuclear hormone receptor that is mainly involved in lipid metabolism. Recent studies have suggested that PPAR- agonists exert vascular protective effects. The present study was designed to characterize vascular function in mice with genetic inactivation of PPAR- in the endothelium. Mice with vascular endothelial cell-specific deletion of the PPAR- gene (ePPAR/ mice) were generated using loxP/Cre technology. ePPAR/ mice were normotensive and did not display any sign of metabolic syndrome. Endothelium-dependent relaxations to ACh and endotheliumindependent relaxations to the nitric oxide (NO) donor diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate were both significantly impaired in the aorta and carotid arteries of ePPAR/ mice (P 0.05). In ePPAR/ mouse aortas, phosphorylation of endothelial NO synthase at Ser1177 was significantly decreased (P 0.05). However, basal levels of cGMP were unexpectedly increased (P 0.05). Enzymatic activity of GTP-cyclohydrolase I and tetrahydrobiopterin levels were also enhanced in ePPAR/ mice (P 0.05). Most notably, endothelium-specific deletion of the PPAR- gene significantly decreased protein expressions of catalase and glutathione peroxidase 1 and resulted in increased levels of H2O2 in the aorta (P 0.05). In contrast, superoxide anion production was unaltered. Moreover, treatment with catalase prevented the endothelial dysfunction and elevation of cGMP detected in aortas of ePPAR/ mice. The findings suggest that increased levels of cGMP caused by H2O2 impair vasodilator reactivity to endogenous and exogenous NO. We speculate that chronic elevation of H2O2 predisposes PPAR--deficient arteries to oxidative stress and vascular dysfunction.

Scientific Abstract:
Peroxisome proliferator-activated receptor (PPAR)-delta is a nuclear hormone receptor that is mainly involved in lipid metabolism. Recent studies have suggested that PPAR-delta agonists exert vascular protective effects. The present study was designed to characterize vascular function in mice with genetic inactivation of PPAR-delta in the endothelium. Mice with vascular endothelial cell-specific deletion of the PPAR-delta gene (ePPARdelta(-/-) mice) were generated using loxP/Cre technology. ePPARdelta(-/-) mice were normotensive and did not display any sign of metabolic syndrome. Endothelium-dependent relaxations to ACh and endothelium-independent relaxations to the nitric oxide (NO) donor diethylammonium (Z)-1-(N,N-diethylamino)diazen-1-ium-1,2-diolate were both significantly impaired in the aorta and carotid arteries of ePPARdelta(-/-) mice (P < 0.05). In ePPARdelta(-/-) mouse aortas, phosphorylation of endothelial NO synthase at Ser(1177) was significantly decreased (P < 0.05). However, basal levels of cGMP were unexpectedly increased (P < 0.05). Enzymatic activity of GTP-cyclohydrolase I and tetrahydrobiopterin levels were also enhanced in ePPARdelta(-/-) mice (P < 0.05). Most notably, endothelium-specific deletion of the PPAR-delta gene significantly decreased protein expressions of catalase and glutathione peroxidase 1 and resulted in increased levels of H2O2 in the aorta (P < 0.05). In contrast, superoxide anion production was unaltered. Moreover, treatment with catalase prevented the endothelial dysfunction and elevation of cGMP detected in aortas of ePPARdelta(-/-) mice. The findings suggest that increased levels of cGMP caused by H2O2 impair vasodilator reactivity to endogenous and exogenous NO. We speculate that chronic elevation of H2O2 predisposes PPAR-delta-deficient arteries to oxidative stress and vascular dysfunction.

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